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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,362	CHEN, JAMES C.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11,12,16-24,36 and 38-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 11-12, 16-24, 36 and 38-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/23/04; 8/25/03;*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/23/04 has been entered.

2. It is noted that the remarks on page 6 of the amendment filed 6/23/04 indicates claims **1, 4-6**, 11, 12, 16-24, 36 and 38-**41** are pending. However, the listing of claims shows that claims 1-6, 11-12, 16-24, 36 and 38-49 are pending.

3. Claims 1-6, 11-12, 16-24, 36 and 38-49 are pending and are being acted upon in this Office Action.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6, 11-12, 16-24, 36 and 38-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method to treat neovascular disease of the eye comprising the method steps of (a) administering a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue in the eye wherein the photosensitizing compound is chlorines, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, porfimer sodium, δ-aminolevulinic acid protoporphyrin, indocyanine green, methylene blue, toluidine blue, texaphyrins, pyropheophorbide, and verteporfin and wherein the targeting moiety is selected from the group consisting of VEGF ligand, antibody or antibody fragment that specifically binds to VEGF receptor, α-vβ3 integrin, the extra-domain B of fibronectin or carcinoembryonic antigen (CEA), (b) allowing non-specifically bound photosensitizing compound to clear from non-target tissues and (c) illuminating the neovascular tissue with light having a wave length or waveband that matches the excitation wave length or waveband of the photosensitizing compound wherein a

combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged, (2) The said method wherein the light is a non-coherent light or a coherent light, (3) the said method wherein the conjugate is incorporated into a liposomal preparation, (4) the said method wherein the photosensitized neovascular tissue is illuminated for a time interval of between about 4 minutes and 72 hours, (5) the said method wherein the photosensitized neovascular tissue is illuminated for a time interval of between about 60 minutes and 148 hours, (6) the said method wherein the photosensitized neovascular tissue is illuminated for a time interval of between about 2 minutes and 24 hours, (7) the said method wherein the neoavascular tissue is treated with a total fluence of the light irradiation from between about 30 Joules and about 25,000 Joules, (8) the said method wherein the neoavascular tissue is treated with a total fluence of the light irradiation from between about 100 Joules and about 20,000 Joules, (9) the said method wherein the neoavascular tissue is treated with a total fluence of the light irradiation from between about 500 Joules and about 10,000 Joules, **does not** reasonably provide enablement for a method to treat any neovascular disease of the eye as set forth in claims 1-6, 11-12, 16-24, 36 and 38-49 by administering all conjugate comprising any photosensitizing compound, such as alkyl ether analogs of chlorins, benzoporphyrin derivatives conjugated to all targeting moiety that binds to abnormal endothelium that lines or composes neovascular target tissue in the eye such as any first member of any binidng pair, any second member of the binding pair is any receptor, any ligand bindable to a receptor, any antigen, any antibody bindable to any antigen, any bispecific antibody construct comprising both ligand and receptor component for a method to treat all neovascular diesease of the eye. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The scope of the claims encompasses a method to treat all neovascular disease of the eye by administering all conjugate comprising any photosensitizing compound conjugated to any targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue of the eye.

The specification discloses only a method to treat neovascular disease of the eye by administering a photosensitizing compound such as the ones listed on page 11 conjugated to a targeting moiety wherein the targeting moiety is selected from the group consisting of VEGF ligand, antibody or antibody fragment thereof that binds to the extracellular domain B (ED-B) of fibronectin, VEGF receptor, $\alpha 3\beta 3$ integrin, CEA antigen and bispecific antibody construct that is a combination of specific VEGF ligand and VEGF receptor on abnormal endothelium that lines or composes neovascular target tissue in the eye, allowing sufficient time, allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light having a wave length or waveband that matches the excitation wave length or waveband of the photosensitizing compound wherein a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged wherein the photosensitized neovascular tissue is illuminated for a time interval of between about 4 minutes and 72 hours, or between about 60 minutes and 148 hours, or between about 2 minutes and 24 hours, and the total fluence of the light irradiation is from between about 30 Joules and about 25,000 Joules, or between about 100 Joules and about 20,000 Joules, or between about 500 Joules and about 10,000 Joules. The specification defines a photosensitizing compound is a any chemical compound that homes to a selected target and absorbs light but are *not limited to*, chlorins, bacteriochlorophylls, phthalocyanines, pophyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD). Other compounds include indocyanine green (lCG); methylene blue; toluidine blue; texaphyrins; and *any other agent* that absorbs light in a range of 500 nm -1100 nm (page 11).

The specification does not teach how to make *all* conjugate comprising any photosensitizing compound such as any benzoporphyrin derivatives, bacteriochlorophyll derivatives, ether analogs of chlorines conjugated to any targeting moiety that selectively binds to all abnormal endothelium for the claimed method because of the following reasons.

There is insufficient guidance as how to make all "derivative" of benzoporphyrin, bacteriochlorophyll and "ether analogs" without the chemical structure, much less about the targeting moiety of the conjugate that binds to abnormal endothelium that lines or composes neovascular target tissue in the eye. The specification defines a photosensitizing compound is a any chemical compound that homes to a selected target and absorbs light but are *not limited to,* chlorins, bacteriochlorophylls, phthalocyanines, pophyrins, purpurpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD). Other compounds include indocyanine green (ICG); methylene blue; toluidine blue; texaphyrins; and *any other agent* that absorbs light in a range of 500 nm -1100 nm (page 11). Given the indefinite number of photosensitizing compound, there is insufficient guidance as to which part of the benzoporphyrin, bacteriochlorophyll or "ether analogs" can be modified and still maintain its function. Further, there is insufficient in vivo working demonstrating that all undisclosed conjugate is effective to treat all neovascular disease of the eye.

Klyashchitsky et al, of record, teach that the property of photosensitizing compound is a very important factor determining the choice of photosensitizing compound to be used as well as the selectivity of photosensitizing compound (See page 1, col. 1, in particular).

Without guidance as to the structure of the photosensitizing compound and the binding specificity of targeting moiety such as the antibody, the ligand (first member of the binding pair), the corresponding receptor (second member of the binding pair), all bispecific antibody construct that further comprises both any ligand component and any receptor component and antigens that are expressed on the abnormal endothelium other than the specific targeting moiety mentioned above, it is unpredictable which undisclosed conjugate comprising the undisclosed photosensitizing compound conjugated to which undisclosed targeting moiety will target to the abnormal endothelium in the eye, let alone the method requires the combination of intensity of light and duration of illumination to arrive at the claimed method to treat all neovascular disease of the eye.

Stryer *et al,* of record, teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages). In the absence of guidance as to the structure of the protein such as the antigen, the receptor, or the ligand, as well as specific component of said receptor and ligand, it is unpredictable which undisclosed antigen, receptor, ligand, and

component of said receptor and component of said ligand would be effective for targeting any photosensitizing compound to the abnormal endothelium as a method for treating any disease.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed antigen, first component of any bindable pair and second component of any bindable pair such as receptor, ligand, antigen, and antibody to said ligand on the abnormal endothelium and bispecific antibody construct further comprising any ligand and any receptor component, it is unpredictable which undisclosed antibody or bispecific antibody would bind specifically to which antigen or which receptor and which ligand, in turn, targeting the photosensitizing compound to the neovascular tissue of the eye as a method to treat neovascular disease of the eye. Given the indefinite number of "photosensitizing compound", "antigen", "bindable pair" of any ligand or receptor, antibody to any ligand, antibody to any receptor and whether said undisclosed ligand, receptor, antigen are expressed on the neovasculature tissue or abnormal endothelium, it is unpredictable which undisclosed ligand, receptor, antigen, antibody to said ligand or receptor would be effective for targeting the photosensitizing compound to the abnormal endothelium as a method to treat neovascular disease of the eye.

Even if the targeted photosensitizing compound is enabled, the light source, the combination of the intensity of light used for the step of illuminating and the duration of illumination to arrive at the total fluence are critical for the claimed method. In fact, the specification on page 10 discloses that "both intensity and duration must be limited to ovoid overtreating the subject". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Because of the lack of sufficient guidance

and predicting which undisclosed targeted photosensitizing compound in which combination of light source, light intensity, and duration of illumination are effective for the claimed method, it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the claimed method.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 6/23/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) applicant is providing a general method of photodynamic therapy to treat neovascular disease of the eye. To limit the claims to specific elements for "photosensitizing compound" or "binding pair" or "endothelial antigen" or "endothelial ligand" or a specific "targeting moiety that selectively binds to abnormal endothelium" would permit those of skill in the art to practice the claimed method, but avoid infringement, merely by substituting different elements to achieve the same outcome, which are known or could be readily identified using the methods described in the specification and known in the art. (2) It would not require undue experimentation lo use the claimed methods in the treatment of neovascular disease of the eye. (3) The level of skilled in the art is high. (4) At the time of filing of the instant application, many photosensitizing compounds were known to those skilled in this art at the time the application was submitted, including hematoporphyrins, porphyrins, chlorins, bacteriochlorins, benzoporphyrins, phthalocyanines, metallo-phlhalocyanines and purpurines and their derivatives; naphthalocyanines, texaphyrins, and other extended tetrapyrroles (Kreimer-Birnbaum, Sem Hematol. 26(2) 1157-1 73 (1 989)). (5) The specification teaches that the function of the photosensitizing compound is to generate singlet oxygen and other reactive species when the photosensitizing compound absorbs light at a wavelength which closely matches the absorption spectra of the photosensitizer (paragraph 10051), which results in impairment or destruction of

the target cells (paragraph (0361). The specification provides exemplary photosensitizing compounds, including any one or combination of chlorins, bacteriochlorophylls, phthalocyanines, porphyrins, purpurins, merocyanines, psoralens, benzo-porphyrin derivatives (BPD), porfimer sodium, indocyanine green (ICG), methylene blue, toluidine blue, texaphyrins and pro-drugs such as J-amino-levulinic acid, which can produce drugs such as protoporphyrin (see paragraph 10361), and pyropheophorbide compounds, bacteriochlorophyll derivatives, alkyl ether analogs of chlorins (see paragraph 10401). (6) The specification teaches how lo Make Anv "Targeted Photosensitizing Compound". The techniques to conjugate a targeting moiety to a photosensitizing compound are well known to those of ordinary skill in this art and are specifically disclosed in the specification. (7) Applicant respectfully submits that the exact structure of the binding pair is not relevant to patentability. Notwithstanding this, the specification provides as specific examples of binding pairs a bindable fragment of the L19 antibody to the ED-B of fibronectin and the ED-B of fibronectin (paragraph (0541), VEGF and VEGF receptor (paragraphs 10581 and 10591), integrin $\alpha v\beta 3$ and anti-integrin $\alpha v\beta 3$ antibody (paragraph (0611), and carcinoembryonic antigen (CEA) and anti-cEA antibody (paragraph 10631). The specification teaches that the antibody is selected to be bindable to endothelial receptors and antigens (10141), and provides as examples antibody elicited to an antigenic determinant on abnormal endothelium, such as the extra domain B of fibronectin (paragraph 0211) and integrins (paragraph 0611) or to antigen associated with choroidal tumor, such as carcinoembryonic antigen (paragraph 1063). The specification teaches, for example, using an intensity of light substantially less that 500 mW/cmz, and that since the total fluence or amount of energy of the light in Joules is divided by the duration of total exposure time in seconds, the longer the amount of time the target is exposed to the irradiation, the greater the amount of total energy or fluence may be used without increasing the amount of the intensity of the light used (see paragraph (050). The specification discloses that selection of a combination of a low intensity light and a prolonged duration of irradiation to activate the photosensitizer reduces the potential for damage to non-target tissue exposed to the irradiation.

However, the scope of the claims encompasses a method to treat all neovascular disease of the eye that requires administering all conjugate comprising any photosensitizing compound conjugated to any targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue of the eye.

The specification discloses only a method to treat neovascular disease of the eye by administering a photosensitizing compound such as the ones listed on page 11 conjugated to a targeting moiety wherein the targeting moiety is selected from the group consisting of VEGF ligand, antibody or antibody fragment thereof that binds to the extracellular domain B (ED-B) of fibronectin, VEGF receptor, $\alpha 3\beta 3$ integrin, CEA antigen and bispecific antibody construct that is a combination of specific VEGF ligand and VEGF receptor on abnormal endothelium that lines or composes neovascular target tissue in the eye, allowing sufficient time, allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light having a wave length or waveband that matches the excitation wave length or waveband of the photosensitizing compound wherein a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged wherein the photosensitized neovascular tissue is illuminated for a time interval of between about 4 minutes and 72 hours, or between about 60 minutes and 148 hours, or between about 2 minutes and 24 hours, and the total fluence of the light irradiation is from between about 30 Joules and about 25,000 Joules, or between about 100 Joules and about 20,000 Joules, or between about 500 Joules and about 10,000 Joules. The specification defines a photosensitizing compound is a any chemical compound that homes to a selected target and absorbs light but are *not limited to*, chlorins, bacteriochlorophylls, phthalocyanines, pophyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD). Other compounds include indocyanine green (lCG); methylene blue; toluidine blue; texaphyrins; and *any other agent* that absorbs light in a range of 500 nm -1100 nm (page 11).

Other than the specific conjugate for the claimed method, there is insufficient guidance as to the structure of all conjugate comprising all photosensitizing compound such as benzoporphyrin "derivative", bacteriochlorophyll "derivative" or "ether analogs" conjugated to all targeting moiety that binds to all ligand, all receptor, all antigen and all bispecific antibody construct comprising any ligand and any receptor on the abnormal endothelium. There is insufficient guidance as how to make all "derivative" of benzoporphyrin, bacteriochlorophyll and "ether analogs" without the chemical structure, much less conjugated to which undisclosed targeting moiety that binds to abnormal endothelium that lines or composes neovascular target tissue in the eye. The specification defines a photosensitizing compound is a any chemical compound that homes to a selected target and absorbs light but are *not limited to*, chlorins,

bacteriochlorophylls, phthalocyanines, pophyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD). Other compounds include indocyanine green (ICG); methylene blue; toluidine blue; texaphyrins; and *any other agent* that absorbs light in a range of 500 nm -1100 nm (page 11). Given the indefinite number of photosensitizing compound, there is insufficient guidance as to which part of the benzoporphyrin, bacteriochlorophyll or "ether analogs" can be modified and still maintain its function.

With regard to the targeting moiety in the conjugate of the claimed method, in order to make the conjugate for the claimed method, the targeting moiety such as the specific antigens, ligands and receptors on the abnormal endothelium in the eye must first be identified, in turn, the antibody such as bispecific antibody or antibody fragment can be made to bind specifically to said antigen, ligand or receptors and then can be linked to the particular photosensitizing compound for the claimed method to treat neovascular disease. Until the specific antigen, ligand, receptor, binding pair and bispecific antibody comprising the specific ligand and receptor that binds to the abnormal endothelium in the eye have been identified, the specification merely extends an invitation to one of skilled in the art to further experimentation to arrive at the claimed invention. Further, there is insufficient in vivo working demonstrating that all undisclosed conjugate is effective to treat all neovascular disease of the eye.

Klyashchitsky et al, of record, teach that the property of photosensitizing compound is a very important factor determining the choice of photosensitizing compound to be used as well as the selectivity of photosensitizing compound (See page 1, col. 1, in particular). Without guidance as to the structure of the photosensitizing compound and the binding specificity of targeting moiety such as the antibody, the ligand (first member of the binding pair), the corresponding receptor (second member of the binding pair) and antigens that are expressed on the abnormal endothelium other than the specific targeting moiety mentioned above, it is unpredictable which undisclosed conjugate comprising the undisclosed photosensitizing compound conjugated to which undisclosed targeting moiety will target to the abnormal endothelium in the eye, let alone the method requires the combination of intensity of light and duration of illumination to arrive at the claimed method to treat all neovascular disease of the eye.

Stryer *et al,* of record, teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages). In the absence of guidance as to the structure of the protein such as the antigen, the receptor, or the ligand, as well as specific component of said

receptor and ligand, it is unpredictable which undisclosed antigen, receptor, ligand, and component of said receptor and component of said ligand would be effective for targeting any photosensitizing compound to the abnormal endothelium as a method for treating any disease.

With regard to antibody, because the specific antigen, receptor or ligand is not disclosed, the binding specificity of the antibody is questionable, in turn, and the targeted photosensitizing compound would bind specifically to the undisclosed antigen on the abnormal endothelium as a method to treat neovascular disease of the eye is not enabled.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed antigen, first component of any bindable pair and second component of any bindable pair such as receptor, ligand, antigen, and any antibody and bispecific antibody construct, there is insufficient in vivo working demonstrating that all photosensitizing compound conjugate are effective for targeting the photosensitizing compound to the abnormal endothelium as a method to treat any neovascular disease of the eye.

Even if the targeted photosensitizing compound is enabled, the light source, the combination of the intensity of light used for the step of illuminating and the duration of illumination to arrive at the total fluence are critical for the claimed method. In fact, the specification on page 10 discloses that "both intensity and duration must be limited to ovoid overtreating the subject". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound.

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predicting which undisclosed targeted photosensitizing compound in which combination of light source, light intensity, and duration of illumination is effective for the claimed method, it

would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the claimed method. For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In response to applicant' argument that specification teaches, for example, using an intensity of light substantially less that 500 mW/cmz, and that since the total fluence or amount of energy of the light in Joules is divided by the duration of total exposure time in seconds, the longer the amount of time the target is exposed to the irradiation, the greater the amount of total energy or fluence may be used without increasing the amount of the intensity of the light used (see paragraph (050), the specification merely invite one skill in the art to further experimentation to arrive at the claimed invention given the indefinite number of conjugate comprising infinite number of photosensitizing compound conjugate to indefinite number of targeting moiety. Further, none of the independent claims recite the specific intensity of light, total fluence and duration of treatment for the claimed method.

In response to applicant' argument that the overall structure of the antigen, receptor or ligand is not relevant to patentability, in order to make the conjugate for the claimed method, the targeting moiety such as the specific antigens, ligands and receptors expressed on the abnormal endothelium in the eye must first be identified, in turn, the antibody such as bispecific antibody or antibody fragment can be made to bind specifically to said antigen, ligand or receptors and then linked to the particular photosensitizing compound for the claimed method to treat neovascular disease. Until the specific antigen, ligand, receptor, binding pair and bispecific antibody comprising the specific ligand and receptor that binds to the abnormal endothelium in the eye have been identified, the specification merely extends an invitation to one of skilled in the art to further experimentation to arrive at the claimed invention. Further, there is insufficient in vivo working demonstrating that all undisclosed conjugate is effective to treat all neovascular disease of the eye.

In contrast to applicant's assertion that there is no evidence to support the Examiner's position that without the guidance as to the structure of the protein such as the antigen, the receptor, or the ligand, it is unpredictable which targeting moiety when conjugate to photosensitizing compound would target the photosensitizing compound to the abnormal endothelium, Klyashchitsky et al, of record, teach that the property of photosensitizing compound is a very important factor determining the choice of photosensitizing compound to be used as well

as the selectivity of the targeting molecule for photodynamic therapy (See page 1, col. 1, abstract, in particular). Stryer *et al,* of record, teach a protein such as antigen, ligand and receptor is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages). Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the indefinite number of undisclosed antigen, first component of any bindable pair and second component of any bindable pair such as receptor, ligand, antigen, and antibody to said ligand on the abnormal endothelium, the binding specificity of any undisclosed antibody and/or bispecific construct further comprising any ligand and receptor component is unpredictable given the indefinite number of undisclosed antigen, ligand, receptor, expressed on the abnormal endothelium of the eye, let alone the targeting the photosensitizing compound to the abnormal endothelium as a method to treat any neovascular disease of the eye.

6. Claims 1-6, 11-12, 16-24, 36, 42, and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of all conjugate comprising all photosensitizing compound, photosensitizing compound such as "derivatives" of benzoporphyrin, bacteriochlorophyll and "ether analogs" conjugated to all targeting moiety wherein the targeting moiety is any ligand (first member of a binding pair), bindable to any receptor (second member of the binding pair), any antibody bindable to any antigen, and any antigen present on abnormal endothelium, any bispecific antibody construct further comprising any ligand and receptor component for a method to treat all neovascular disease of the eye, such as diabetic retinopathy, macular degeneration, and tumor as set forth in claims 1-6, 11-12, 16-24, 36, 42, and 46-49.

The specification discloses only a method to treat neovascular disease of the eye by administering a photosensitizing compound such as the ones listed on page 11 conjugated to a targeting moiety wherein the targeting moiety is selected from the group consisting of VEGF ligand, antibody or antibody fragment thereof that binds to the extracellular domain B (ED-B) of

fibronectin, VEGF receptor, α3β3 integrin, CEA antigen and bispecific antibody construct that is a combination of specific VEGF ligand and VEGF receptor on abnormal endothelium that lines or composes neovascular target tissue in the eye, allowing sufficient time, allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue; and illuminating the neovascular tissue with light having a wave length or waveband that matches the excitation wave length or waveband of the photosensitizing compound wherein a combination of an intensity of light used for the step of illuminating and a duration of illumination is selected to produce a total fluence of irradiation such that the neovascular target tissue is destroyed and the non-target tissue through which the light passes remains undamaged wherein the photosensitized neovascular tissue is illuminated for a time interval of between about 4 minutes and 72 hours, or between about 60 minutes and 148 hours, or between about 2 minutes and 24 hours, and the total fluence of the light irradiation is from between about 30 Joules and about 25,000 Joules, or between about 100 Joules and about 20,000 Joules, or between about 500 Joules and about 10,000 Joules. The specification defines a photosensitizing compound is a any chemical compound that homes to a selected target and absorbs light but are *not limited to*, chlorins, bacteriochlorophylls, phthalocyanines, pophyrins, purpurins, merocyanines, psoralens, benzoporphyrin derivatives (BPD). Other compounds include indocyanine green (lCG); methylene blue; toluidine blue; texaphyrins; and *any other agent* that absorbs light in a range of 500 nm -1100 nm (page 11).

Other than the specific conjugate for the claimed method, there is insufficient guidance as to the structure of all conjugate comprising all photosensitizing compound such as benzoporphyrin "derivative", bacteriochlorophyll "derivative" or "ether analogs" conjugated to all targeting moiety that binds to all ligand, all receptor, all antigen and all bispecific antibody construct comprising any ligand and any receptor on the abnormal endothelium. Further, in order to make the conjugate for the claimed method, the targeting moiety such as the specific antigens, ligands and receptors on the abnormal endothelium in the eye must first be identified, in turn, the antibody such as bispecific antibody or antibody fragment can be made to bind specifically to said antigen, ligand or receptors and then linked to the particular photosensitizing compound for the claimed method to treat neovascular disease.

With the exception of the specific method to treat neovascular disease of the eye using the specific target photosensitizing compound, there is inadequate written description about the structure and binding specificity of all conjugate comprising any undisclosed photosensitizing compound such as benzoporphyrin "derivative", bacteriochlorophyll "derivative" or "ether

analogs" conjugated to all targeting moiety that binds to all ligand, all receptor, all antigen and all bispecific antibody construct comprising any ligand and any receptor on the abnormal endothelium.

The specification does not adequately describe the genus of conjugate to be used by the claimed method. The exemplary embodiments nor the specification's general method appears to describe the structural features of photosensitizing compound and the structural features of the targeting moiety within the conjugate that are common to the genus. Further, the conjugate comprising verteporfin conjugated to antibody that binds to ED-B of fibronectin, bezoporphyrin derivative conjugated to VEGF (ligand) or antibody to CEA antigen, and texaphyrin conjugated to antibody that binds to $\alpha v\beta 3$ integrin do not appear to be a representative number of species within the genus for the claimed method. The specification provides no structural description of all ligand, receptor, much less about the binding specificity of the antibody to antigen and antigen in the targeting moiety of the conjugate other than the ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the conjugate in the claimed method look like. Further, there is inadequate written description about the method step wherein a combination of any intensity of light use for the step of illuminating and any duration of illumination such as at 4 minutes, at least 20 minutes, at least 1 hour and at least 24 hours along with any undisclosed target photosensitizing compound. In fact, the specification on page 10 discloses that "both intensity and duration must be limited to ovoid overtreating the subject". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound in any combination of light intensity and duration of illumination. Finally, the method step of allowing non-specifically bound photosensitizing compound to clear from collateral tissues is missing in the claims which clearly required by the disclosure (See examples 1-4).

For reasons indicated above, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly*

and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 6/23/04 have been fully considered but are not found persuasive.

Applicants' position is that the specification defines the properties requisite for activity (binding to an upregulated endothelial receptor or an endothelial receptor found on an abnormal blood vessel wall). The applicantion provides specific working examples that include four different ligands (ED-B of fibronectin, VEGF, αvβ3 integrin, and carcinoembryonic antigen, and 2 VEGF receptor. Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed.

However, the scope of the claims encompasses a method to treat all neovascular disease of the eye that requires administering *all* conjugate comprising any photosensitizing compound conjugated to any targeting moiety that selectively binds to abnormal endothelium that lines or composes neovascular target tissue of the eye.

Other than the specific conjugate for the claimed method, there is insufficient written description about the binding specificity of the targeting moiety in the conjugate, all photosensitizing compound such as benzoporphyrin "derivative", bacteriochlorophyll "derivative" or "ether analogs" conjugated to all targeting moiety that binds to all ligand, all receptor, all antigen and all bispecific antibody construct comprising any ligand and any receptor on the abnormal endothelium. Further, In order to make the conjugate for the claimed method, the targeting moiety such as the specific antigens, ligands and receptors on the abnormal endothelium in the eye must first be identified, in turn, the antibody such as bispecific antibody or antibody fragment can be made to bind specifically to said antigen, ligand or receptors and then linked to the particular photosensitizing compound for the claimed method to treat neovascular disease.

With the exception of the specific method to treat neovascular disease of the eye using the specific target photosensitizing compound, there is inadequate written description about the

structure of all conjugate comprising any undisclosed photosensitizing compound such as benzoporphyrin "derivative", bacteriochlorophyll "derivative" or "ether analogs" conjugated to all targeting moiety that binds to all ligand, all receptor, all antigen and all bispecific antibody construct comprising any ligand and any receptor on the abnormal endothelium.

The specification does not adequately describe the genus of conjugate to be used by the claimed method. The exemplary embodiments nor the specification's general method appears to describe the structural features of photosensitizing compound and the structural features of the targeting moiety within the conjugate that are common to the genus. Further, the conjugate comprising verteporfin conjugated to antibody that binds to ED-B of fibronectin, bezoporphyrin derivative conjugated to VEGF (ligand) or antibody to CEA antigen, and texaphyrin conjugated to antibody that binds to $\alpha v\beta 3$ integrin do not appear to be a representative number of species within the genus for the claimed method. The specification provides no structural description of all ligand, receptor, much less about the binding specificity of the antibody to antigen and antigen in the targeting moiety of the conjugate other than the ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the conjugate in the claimed method look like. Further, there is inadequate written description about the method step wherein a combination of any intensity of light use for the step of illuminating and any duration of illumination such as at 4 minutes, at least 20 minutes, at least 1 hour and at least 24 hours along with any undisclosed target photosensitizing compound. In fact, the specification on page 10 discloses that "both intensity and duration must be limited to ovoid overtreating the subject". Given the lack of upper limit for the duration of illumination as set forth in claim 1 and 18-21, it is not clear if the claimed method as written is effective for treating neovascular disease without impairing or destroying other tissues. The recitation of "at least" 4 minutes (claim 18), "at least" 20 minutes (claim 19), "at least" 1 hour (claim 20) and "at least" 24 hours (claim 21) merely requires that lower limit of illumination be at least 4, 20, 1 and 24 hours, respectively. However, there is insufficient guidance for the intensity of the light used for the claimed method given the infinite number of undisclosed targeted photosensitizing compound in any combination of light intensity and duration of illumination. Finally, the method step of allowing non-specifically bound photosensitizing compound to clear from collateral tissues is missing in the claims which clearly required by the disclosure (See examples 1-4).

For reasons indicated above, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus,

Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. Claims 1-6, 11-12, 16-24, 36, and 38-49 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

"A method ...including a wavelength corresponding **at least in part with the characteristic light absorption wavelength of the photosensitizing compound**" in claim 1 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 8/25/03 do not provide a clear support for the said phrase.

"The method ....at least 4 minutes" in claim 18 represents a departure from the specification and the claims as originally filed because the upper limit is not specified. The specification on page 14 paragraph 048 discloses the duration of illumination period is between about 4 minutes and 72 hours.

"The method ....at least 20 minutes" in claim 19 represents a departure from the specification and the claims as originally filed because the upper limit is not specified.

"The method ....at least 1 hour" in claim 20 represents a departure from the specification and the claims as originally filed because the upper limit is not specified. The specification on page 14 paragraph 048 discloses the duration of illumination period is between about 60 minutes and 148 hours. And preferably is between about 2 hours and 24 hours.

"The method ....at least 24 hours" in claim 21 represents a departure from the specification and the claims as originally filed because the upper limit is not specified. The specification on page 14 paragraph 048 discloses the duration of illumination period is between about 60 minutes and 148 hours. And preferably is between about 2 hours and 24 hours.

"The method ...total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2" in claim 22 represents a departure from the specification and the claims as originally

filed because the specification does not provide a clear support for the narrow range between about 240 J/cm^2 to about 900 J/cm^2. The specification discloses on page 14 paragraph 049 that the total fluence of light used for irradiating is between about 30 Joules and about 25,000 Joules, or between about 100 Joules and about 20,000 Joules, or between about 500 Joules and about 10,000 Joules.

"The method ...of at least 4 minutes...25,000 J/cm^2" in claim 45 represents a departure from the specification and the claims as originally filed because the upper limit is not specified.

"The method...with total fluence of light irradiation from between about 240 J/cm^2 to about 900 J/cm^2" in claim 46 represents a departure from the specification and the claims as originally filed because the specification does not provide a clear support for the narrow range between about 240 J/cm^2 to about 900 J/cm^2 as now claimed.

The "benoporphyrin derivatives (BPD)" in claim 42 is improper Markush group because benoporphyrin derivatives is recited twice in the claim.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3-6, 11-12, 17-21, 36, and 41-43 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,756,541 (of record, May 1998; PTO 1449) as evident by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892).

The '541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a conjugate comprising photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) or low density lipoprotein ligand that binds to the LDL receptor on the abnormal endothelium (See col. 3, lines 42-48, in particular), allowing sufficient time after administering the reference conjugate to permit the binding of the conjugate the to the specific ocular tissue being targeted such as about 1 minute to about 2 hours (See col. 4, line 65 bridging col. 5, lines 1-4, claim 3 of '541 patent, in particular) which inherently also allows non-specifically bound conjugate to clear from

non-target tissue, and illuminating the neovascular tissue with light from a coherent Argon dye laser (See col. 5, lines 45-50, in particular) that corresponds with the wavelength of the photosensitizing agent such as between about 550 and 695 nm (See col. 4, lines 35-45, in particular) for a period to activate the reference photosensitized compound wherein the neovascular tissue is treated with a total fluence of light irradiation from 50 J/cm 2 to 150 J/cm^2 (See col. 5, lines 5-8, claim 2 of '541 patent, in particular) for a duration such as 90-270 seconds of irradiation (See col. 5, lines 5-8, in particular). The reference method wherein the neovascular tissue is choroidal vessels (See col. 1, lines 28, col. 2, line 1-2, in particular). The reference method further comprises the step of illuminating the neovasculature tissue with laser light for a period of time such as 90 second to cause damage to the neovasculature tissue without impairing or destroying other tissue (See column 5, lines 10-12 and lines 21, claims of '541 patent, in particular). The reference method wherein the reference targeted photosensitizing compound is formulated in liposome (See col. 3, line 40, in particular). Claim 18 is included in this rejection because the reference method wherein the photosensitized neovascular tissue is illuminated for 270 seconds (See col. 5, line 7-8, in particular) which is equivalent to at least 4 minutes. Claims 19-21 are included in this rejection because the '541 patent teaches the various parameters used for effective selective photodynamic therapy are interrelated and should be adjusted to produce significant enhancement of visual acuity without significant damage to the eye tissue (See col. 4, lines 22-30, in particular). Claim 36 is included in this rejection because the instruction to a person to conduct the claimed method at the time the invention was made is within the teachings of the '541 patent. Claim 43 is included in this because verteporfin is a generic name as evident by the teaching of Kramer et al (abstract, in particular) for benzoporphyrin derivative monoacid ring A, BPD-MA as taught by the '541 patent (See col. 1, line 44-45, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed 6/23/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) Strong et al. does not disclose a method to treat neovascular disease of the eye that includes allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. Strong et al. does not disclose clearance of the photosensitizer from non-target tissue. (2) Strong et al does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-target tissue. (3) Strong

et al discloses that its method results in deleterious effects of the tissue immediately surrounding the activated photosensitizer, making no distinction between target and non-targeted tissue and discloses that mild retina whitening occurs (See col. 2, lines 31-33 and col. 5, lines 10-13).

In contrast to applicant's assertion that the reference does not disclose a method to treat neovascular disease of the eye that includes allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, the '541 patent teaches a method to treat neovascular disease of the eye such as macular degeneration that includes allowing sufficient time after administering the reference conjugate to permit the binding of the conjugate the to the specific ocular tissue being targeted such as about 1 minute to about 2 hours (See col. 4, line 65 bridging col. 5, lines 1-4, claim 3 of '541 patent, in particular). The reference step inherently allows non-specifically bound conjugate to clear from non-target tissue such that without damage to the eye tissue.

In contrast to applicant's assertion that Strong et al does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-target tissue, the '541 patent teaches that the reference method illuminates the neovascular tissue with light from a coherent Argon dye laser (See col. 5, lines 45-50, in particular) that corresponds with the wavelength of the photosensitizing agent such as between about 550 and 695 nm (See col. 4, lines 35-45, in particular) for a period to activate the reference photosensitized compound wherein the neovascular tissue is treated with a total fluence of light irradiation from 50 J/cm 2 to 150 J/cm^2 (See col. 5, lines 5-8, claim 2 of '541 patent, in particular) for a duration such as 90-270 seconds of irradiation (See col. 5, lines 5-8, in particular). The '541 patent teaches the various parameters used for effective selective photodynamic therapy are interrelated and should be adjusted to produce significant enhancement of visual acuity without significant damage to the eye tissue (See col. 4, lines 22-30, in particular).

In response to applicant's argument that Strong et al discloses that its method results in deleterious effects of the tissue immediately surrounding the activated photosensitizer, making no distinction between target and non-targeted tissue and discloses that mild retina whitening occurs, the claimed method as recited in claim 1 is not different than the method of '541 patent because the specific wavelength, the duration and total fluence are not recited in the claim.

10. Claims 1, 3-6, 11, 18, 36, 42-43 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892).

Kramer *et al* teach a method of treating unwanted choroidal neovasculature (CNV) such as diabetic retinopathy, age-related macular degeneration, corneal neovascularization and ocular tumor (See entire document, page 437, in particular) by administering to a mammal such as monkeys a photosensitizing compound such as benzoporphyrin derivative (BDP) or verteporfin conjugated to a targeting moiety such as liposome or LDL that selectively binds to LDL receptor and accumulate in rapidly proliferating endothelium of the eye (See page 428, col. 1, par. 2-3, in particular), allowing sufficient time such as 10, 20, 30, 40, 50, 60 and 80 minutes after dye injection to permit the non-specific bound conjugate to clear from non-target tissue (See page 433, col. 1, page 435, col. 2, last par., in particular) and illuminating the neovascular tissue with light at a wavelength such as 692 nm (see page 429, col. 1, par. 2, in particular) that matches the light absorption wavelength (see page 428, col. 1, par. 3, in particular) for a duration such as 4 minutes 9 second which is at least 4 minutes (see page 437, col. 1, in particular) at an intensity or fluence of 150 J/cm^2 which is between about 30 J/cm^2 to about 25,000 J/cm^2 (see page 437, col. 1, in particular). The reference method wherein the light is coherent laser light (See page 429, Photodynamic Therapy, in particular). Thus, the reference teachings anticipate the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 2, 11 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (of record, May 1998; PTO 1449) as evident by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of Klyashchitsky *et al* (or record, J of Controlled Release 29(1-2): 16-16, 1994; PTO 892) and Boulton *et al* (of record, Br J Opthlalmol 82: 561-568, 1998; PTO 892), Blaauwgeers *et al* (of record, Am J Pathology 155(2): 421-428, 1999; PTO 892), or Prewett *et al* (of record, Cancer Res 59: 5209-18, 1999; PTO 892).

The teachings of the '541 patent as evident by Kramer *et al* have been discussed supra.

The claimed invention in claim 2 differs from the teachings of the references only that the method wherein the light is non-laser light.

The claimed invention in claim 11 differs from the teachings of the references only in that the method wherein the targeting moiety is an VEGF (first member) bindable to a VEGF receptor.

The claimed invention in claim 38 differs from the teachings of the references only that the targeted photosensitizing compound is conjugated to an antibody that binds to a VEGF receptor.

The claimed invention in claim 39 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF.

The claimed invention in claim 40 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF receptor.

Klyashchitsky *et al* teach photodynamic therapy (PDT) is based on the ability of porphyrins and other photosensitizers to be accumulated preferentially in cells such as tumors and to generate singlet oxygen when activated by visible light (See abstract, in particular). Klyashchitsky *et al* further teach that targeting molecule such as antibody that is specific for antigen or the receptor on neovascular disease such as tumor is efficient and useful for delivery of PDT selectively to the tumor cells (See abstract, in particular).

Boulton *et al* teach VEGF plays a role in neovascularization in diabetic retinopathy and antibody to VEGF detects VEGF in endothelial cell in the retinal or choroidal of diabetic retina (see Abstract, Table 1, page 563, column 1, first paragraph, in particular). Boulton *et al* teach VEGF binds to VEGF receptors on endothelial cells such as inner retina (See page 566, column 2, first full paragraph, in particular).

Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriodal capillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Blaauwgeers *et al* teach that unregulated VEGF secretion by RPE plays a role in neovascularization.

Prewett *et al* teach antibody such as DC101 that binds specifically to Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) or LDL that is conjugated to the photosensitizing compound as taught by the '541 patent for the VEGF that plays a role in neovascularization in diabetic retinopathy as taught by Boulton *et al,* or the antibody to the VEGF receptor as taught by Prewett *et al* or the VEGF receptor as taught by Blaauwgeers *et al* for a method to treat neovascular disease by targeting the photosensitizing compound to treat neovascular disease as taught by the '541 patent and Klyashchitsky *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klyashchitsky *et al* teach that targeting molecule such as antibody that is specific for antigen or receptor is efficient and useful for selective delivery of PDT to the site of interest (See abstract, in particular). Prewett *et al* teach antibody such as DC101 that binds specifically to the Flk-1/KDR VEGF receptor and is useful for inhibiting angiogenesis or neovascularization (See entire document, abstract, Fir 2, in particular). Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriodcapillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Boulton *et al* teach that VEGF binds to VEGF receptors on endothelial cells such as inner retina play a role in neovascularization in diabetic retinopathy (See page 566, column 2, first full paragraph, abstract, in particular). The '541 patent teaches that administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) is useful for treating neovascular disease of the eye such as age-related macular degeneration (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular).

Applicants' arguments filed 6/23/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) strong et al are discussed above. (2) Boulton et al does not teach or suggest a conjugate that includes a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium. (3) Boulton et al does not

disclose allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue. (4) Blaauwgeers et al does not teach or suggest treating neovascular disease using a photosensitizing compound nor does the reference teach or suggest a conjugate that include a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium.

In contrast to applicant's assertion that the reference does not disclose a method to treat neovascular disease of the eye that includes allowing sufficient time to permit the non-specifically bound conjugate to clear from non-target tissue, the '541 patent teaches a method to treat neovascular disease of the eye such as macular degeneration that includes allowing sufficient time after administering the reference conjugate to permit the binding of the conjugate the to the specific ocular tissue being targeted such as about 1 minute to about 2 hours (See col. 4, line 65 bridging col. 5, lines 1-4, claim 3 of '541 patent, in particular). The reference step inherently allows non-specifically bound conjugate to clear from non-target tissue such that without damage to the eye tissue.

In contrast to applicant's assertion that Strong et al does not disclose selecting a combination of an intensity of light used for the step of illuminating and a duration of illumination to achieve target tissue destruction without damage to non-target tissue, the '541 patent teaches that the reference method illuminates the neovascular tissue with light from a coherent Argon dye laser (See col. 5, lines 45-50, in particular) that corresponds with the wavelength of the photosensitizing agent such as between about 550 and 695 nm (See col. 4, lines 35-45, in particular) for a period to activate the reference photosensitized compound wherein the neovascular tissue is treated with a total fluence of light irradiation from 50 J/cm 2 to 150 J/cm^2 (See col. 5, lines 5-8, claim 2 of '541 patent, in particular) for a duration such as 90-270 seconds of irradiation (See col. 5, lines 5-8, in particular). The '541 patent teaches the various parameters used for effective selective photodynamic therapy are interrelated and should be adjusted to produce significant enhancement of visual acuity without significant damage to the eye tissue (See col. 4, lines 22-30, in particular).

In response to applicant's argument that Strong et al discloses that its method results in deleterious effects of the tissue immediately surrounding the activated photosensitizer, making no distinction between target and non-targeted tissue and discloses that mild retina whitening occurs, the claimed method as recited in claim 1 is not different than the method of '541 patent because the specific wavelength, the duration and total fluence are not recited in the claim.

In response to arguing against references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. Further, Boulton *et al* teach VEGF plays a role in neovascularization in diabetic retinopathy and antibody to VEGF detects VEGF in abnormal endothelium in the retinal or choroidal of diabetic retina (see Abstract, Table 1, page 563, column 1, first paragraph, in particular). Boulton *et al* teach VEGF binds to VEGF receptors on endothelial cells such as inner retina (See page 566, column 2, first full paragraph, in particular).

In response to applicant's argument that Blaauwgeers et al or Klyashchitsky et al or Prewett et al does not teach or suggest treating neovascular disease using a photosensitizing compound nor does the reference teach or suggest a conjugate that include a photosensitizing compound conjugated to a targeting moiety that selectively binds to abnormal endothelium, The '541 patent teaches a method to treat neovascular disease of the eye such as age-related macular degeneration comprising administering a conjugate comprising photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) or low density lipoprotein ligand that binds to the LDL receptor on the abnormal endothelium (See col. 3, lines 42-48, in particular).

The claimed invention in claim 2 differs from the teachings of the references only that the method wherein the light is non-laser light.

The claimed invention in claim 11 differs from the teachings of the references only in that the method wherein the targeting moiety is an VEGF (first member) bindable to a VEGF receptor.

The claimed invention in claim 38 differs from the teachings of the references only that the targeted photosensitizing compound is conjugated to an antibody that binds to a VEGF receptor.

The claimed invention in claim 39 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF.

The claimed invention in claim 40 differs from the teachings of the reference only that the targeted photosensitizing compound is conjugated to VEGF receptor.

Klyashchitsky *et al* teach photodynamic therapy (PDT) is based on the ability of porphyrins and other photosensitizers to be accumulated preferentially in cells such as tumors and to generate singlet oxygen when activated by visible light (See abstract, in particular). Klyashchitsky *et al* further teach that targeting molecule such as antibody that is specific for antigen or the receptor on neovascular disease such as tumor is efficient and useful for delivery of PDT selectively to the tumor cells (See abstract, in particular).

Boulton *et al* teach VEGF plays a role in neovascularization in diabetic retinopathy and antibody to VEGF detects VEGF in endothelial cell in the retinal or choroidal of diabetic retina (see Abstract, Table 1, page 563, column 1, first paragraph, in particular). Boulton *et al* teach VEGF binds to VEGF receptors on endothelial cells such as inner retina (See page 566, column 2, first full paragraph, in particular).

Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choroids capillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Blaauwgeers *et al* teach that unregulated VEGF secretion by RPE plays a role in neovascularization.

Prewett *et al* teach antibody such as DC101 that binds specifically to Flk-1/KDR VEGF receptor and the reference antibody is useful for inhibits angiogenesis (See entire document, abstract, Fir 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) or LDL that is conjugated to the photosensitizing compound as taught by the '541 patent for the VEGF that plays a role in neovascularization in diabetic retinopathy as taught by Boulton *et al,* or the antibody to the VEGF receptor as taught by Prewett *et al* or the VEGF receptor as taught by Blaauwgeers *et al* for a method to treat neovascular disease by targeting the photosensitizing compound to treat neovascular disease as taught by the '541 patent and Klyashchitsky *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Klyashchitsky *et al* teach that targeting molecule such as antibody that is specific for antigen or receptor is efficient and useful for selective delivery of PDT to the site of interest (See abstract, in

particular). Prewett *et al* teach antibody such as DC101 that binds specifically to the Flk-1/KDR VEGF receptor and is useful for inhibiting angiogenesis or neovascularization (See entire document, abstract, Fir 2, in particular). Blaauwgeers *et al* teach VEGF receptor such as VEGFR-2 or KDR and VEGFR-3 (flt-4) are localized to the choriods capillaries (CC) endothelium facing the retinal pigment epithelium layer whereas VEGFR-1 is found in the inner CC on other choroidal vessel (See abstract, in particular). Boulton *et al* teach that VEGF binds to VEGF receptors on endothelial cells such as inner retina play a role in neovascularization in diabetic retinopathy (See page 566, column 2, first full paragraph, abstract, in particular). The '541 patent teaches that administering a photosensitizing compound such as chlorine and green porphyrin (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular) coupled to a specific binding ligand such as antibody that binds to the target ocular tissue (See column 3, lines 29-31, column 4, lines 11-13, in particular) is useful for treating neovascular disease of the eye such as age-related macular degeneration (See claim 6 of '541, column 2, line 15, Fig 1, column 35-60, in particular).

13. Claims 1, 11, and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (of record, May 1998; PTO 1449) as evident by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of US Pat 6,270,749 B1 (filed June 10, 1999; PTO 892).

The teachings of the '541 patent as evident by Kramer *et al* have been discussed supra.

The claimed invention in claim 11 differs from the teachings of the references only in that the method wherein the targeting moiety is an antibody bindable to an antigen such as VEGF present on abnormal endothelium.

The claimed invention in claim 43 differs from the teachings of the references only in that the method to treat neovascular disease wherein the photosensitizing compound is texaphyrin.

The '749 patent teaches a method of treating unwanted choroidal neovasculature such as aged related macular degeneration (See abstract, col. 6, lines 25-42, col. 23, lines 10-11, in particular) comprising administering to the mammal an effective amount of a conjugate comprising a photosensitizing compound such as lutetium texaphyrin or LuT2BET, or benzoporphyrin derivatives (See col. 2, lines 65-70, in particular) conjugated to a targeting moiety such as a monoclonal antibody to VEGF on abnormal endothelium (See col. 10, lines 48-50, col. 19, lines 30-45, in particular) and irradiating the choroidal neovasculature with laser light

(see col. 21, lines 5-8, in particular) such that the light is occlude the choroidal neovasculature (See col. 25, line 31, in particular). The advantage of the reference method is that the reference PDT treatment is more selective over other technique such as photocoagulation (See col. 25, lines 35-37, in particular). The advantages of texaphyrins are that it is more versatile for use in humans as compared to porphyrins (See abstract, in particular), texaphyrins are cleared quickly from the body and no toxicity to the eye has been observed (See col. 5, lines 8-16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the photosensitizing compound such as chlorine and green porphyrin in the conjugate as taught by the '541 for the photosensitizing compound such as texaphyrin as taught by the '749 patent for a method to treat neovascular disease such as macular degeneration as taught by the '541 patent and the '749 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to substitute the chlorine and green porphyrin in the conjugate because the '749 patent teaches that the advantages of texaphyrins are that it is more versatile for use in humans as compared to porphyrins (See abstract, in particular), and texaphyrins are cleared quickly from the body and no toxicity to the eye has been observed (See col. 5, lines 8-16, in particular).

14. Claims 1, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,756,541 (of record, May 1998; PTO 1449) as evident by Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of WO 97/31582 (September 4, 1997; PTO 1449).

The teachings of the '541 patent as evident by Kramer et al have been discussed supra.

The claimed invention in claim 44 differs from the teachings of the references only in that the method to treat neovascular disease wherein the photosensitizing compound is indocyanine green.

The WO 97/31582 publication teaches a photosensitizing compound such as indocyanine green for photodynamic therapy in treating neovascular disease such as tumor or induction of photocoagulation (See entire document, page 1-2, in particular). The indocyanine dye (ICG) has been use in humans (page 1 in particular), and effective to destroyed the irradiated tissue and eliminating proliferating cancer cells without induce scarring, and other adverse conditions (See summary of invention, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the photosensitizing compound such as chlorine and green porphyrin in the conjugate as taught by the '541 for the indocyanine green as taught by the WO 97/31582 publication for a method to treat neovascular disease such as macular degeneration as taught by the '541 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to substitute the chlorine and green porphyrin in the conjugate because the WO 97/31582 publication teaches that the indocyanine dye (ICG) has been use in humans (page 1 in particular), and effective to destroyed the irradiated tissue and eliminating proliferating cancer cells without induce scarring, and other adverse conditions (See summary of invention, in particular).

15. Claims 16, 22-24 and 46-49 are free of art.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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